Remarks

I. Status of the Claims

Claims 58-71 are pending and under examination. Claims 1-20, 29-45, and 54-57 are withdrawn from consideration. Prior to the instant Office Action, claims 58, 62-66, and 68-71 were allowed. *See* Office Action, 08/29/2005, p. 1. Claims 58-71 stand rejected in the current Office Action.

II. Formal matters

The Office objects to claim 69 for a typographical error. Claim 69 has been amended to delete the space between the 4 and the 2, as indicated in the claim amendments.

III. Enablement Rejections under 35 U.S.C. § 112, first paragraph

The Office rejects claims 58-71 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. According to the Office, "Applicant does not shown any fragment comprising the amino acids 42-60, or comprising amino acids 42-88 of SEQ ID NO:2 have specific inhibitory activity for P-selectin/PSGL-1 binding." Office Action, 10/4/2006, p. 4. The Office also asserts that "Applicant has not provided teachings to indicate that such binding inhibition induced by the PSGL-1 fragment is sufficient to inhibit leukocyte/endothelial cell interaction, and is sufficient to reduce inflammation in any recited disease." *Id.* at 4. The Office states that Ridger *et al.* "L- And P-Selectins Collaborate To Support Leukocyte Rolling In Vivo When High-Affinity P-Selectin-P-Selectin Glycoprotein Ligand-1 Interaction Is Inhibited," Am J Pathol 166(3):945-52 (2005) ("Ridger") teaches that "leukocyte rolling can continue in the absence of optimal

P-selectin/PSGL-1 interaction." *Id.* The Office concludes that the specification fails to provide sufficient guidance to allow the artisan to reduce inflammation in subjects having all those diseases recited in the claims. *Id.* at 5.

Applicants respectfully traverse the rejection of claims 58-71, as the specification provides sufficient guidance for the skilled artisan to practice the invention. As recognized by the Office, the specification describes numerous P-selectin ligand fragments, and presents the results of binding studies of those fragments with P-selectin and E-selectin. *Id.* at 5. *See* specification Figures 12, 23, and 24. Also noted by the Office, the specification teaches the ability of P-selectin ligand fragments to inhibit ligand binding. *Id.* at 5. *See* specification, Figures 13-17. Based on these observations, the specification concludes that P-selectin ligand proteins "comprising as little as amino acids 42-60 of SEQ ID NO: 2 are capable of binding to P-selectin." Specification, page 49, lines 28-30. Thus, the specification identifies a minimal region of SEQ ID NO. 2, amino acids 42-60, which is sufficient to mediate the binding of PSGL-1 to P-selectin.

Moreover, the results in Figure 30, described in Example 13, show that peptides comprising fragments of amino acids 42-60 of SEQ ID NO: 2 are sufficient to inhibit P-selectin binding. Specifically, Figure 30 demonstrates that a sequence comprising amino acids 42-56 inhibits P-selectin binding. While it is true that Example 13 does not employ a sequence that includes amino acids 57-60 of SEQ ID NO: 2, there is nothing to suggest that these four additional amino acids would prevent the protein from inhibiting P-selectin binding. Similarly, there is no suggestion that the additional amino

acids included in the protein comprising amino acids 42-88 would prevent the inhibition of P-selectin binding. On the contrary, it is reasonable to expect that a protein that comprises the amino acids sufficient to mediate P-selectin binding would retain this activity regardless of additional amino acids.

The specification describes a system for assaying the interaction between cells expressing P-selectin and P-selectin ligand, and this system would enable the skilled artisan to measure the inhibitory effects of PSGL-1 fragments. The Office contends that the *in vitro* assay system described in the specification "is a completely different system" from Theroret *et al.* "P-Selectin Antagonism With Recombinant P-Selectin Glycoprotein Ligand-1 (rPSGL-Ig) Inhibits Circulating Activated Platelet Binding To Neutrophils Induced By Damaged Arterial Surfaces," J Pharmacol Exp Ther. 298(2):658-64 (2002) ("Theoret"), which "can only detect binding between P-selectin and PSGL-1." *Id.* at 6. The Office states that "Theoret teaches that a soluble form of PSGL-1 (rPGSL-Ig) can inhibit the interaction between leukocytes/platelets and endothelial cells," but "Theoret does not confirm any PSGL-1 fragments other than rPSGL-Ig having the inhibitory activity for the interaction between leukocytes/platelets and endothelial cells." *Id.*

Applicants disagree with the meaning of Theoret, and with the suggestion that the system of Theoret is superior to the system described in the specification. As noted above, the specification identifies the region of PSGL-1 that is sufficient to mediate binding to P-selectin, and demonstrates that peptides comprising this region inhibit the interaction between P-selectin and ligand in an *in vitro* binding assay. Moreover, Example 6 of the specification further demonstrates that PSGL-1 can mediate cell-cell

interactions and that this interaction can be blocked by an anti-P-selectin antagonist. Thus the specification teaches that a PSGL-1 protein that comprises the region sufficient for P-selectin binding can mediate cell-cell interactions, which was demonstrated by the experimental system taught in the specification. These results parallel the results of Theoret, who showed that addition of P-selectin antagonists, including rPSGL-1g, anti-P-selectin and PSGL-1 blocking antibodies, inhibited cell-cell interactions. *See* Figure 5. It is true that the system of Theoret attempts to more closely mimic the situation *in vivo* by conducting binding studies in Plexiglas tubes that resemble blood vessels and using excised arterial segments. *See* Materials and Methods. However, because the results in Theoret are parallel those of the specification, this fact tends to strengthen the results obtained with the system taught in the specification. Theoret confirms the teaching of the specification by obtaining similar results with a different experimental system.

The reliance on Ridger to find lack of enablement is misplaced. The Office appears to conclude that the claims are not enabled because Ridger teaches that other mechanisms may allow leukocytes to roll even when PSGL-1/P-selectin interaction is suboptimal. *Id.* at 4-5. However, the claims recite "reducing inflammation" and there is nothing in the specification that teaches that such reduction requires the complete cessation of leukocyte rolling. Moreover, the claims are directed to "a therapeutically effective amount" of the claimed proteins. The specification defines this term as the amount "that is sufficient to show a meaningful patient benefit, i.e., healing of chronic conditions characterized by P-selectin- or E-selectin-mediated cellular adhesion or

increase the rate of healing those conditions." The specification does not teach that the invention must completely eliminate inflammation or leukocyte rolling. Thus, even if some leukocyte rolling occurred after administration, inflammation would still be reduced by the elimination of a percentage of leukocyte rolling.

The Office also rejects claims 58-71 on the grounds that the specification teaches fusion proteins comprising (a) amino acid sequence comprising amino acid 42 to amino acid 60 of SEQ ID NO: 2, and (b) a non-P selectin ligand amino acid sequence, but has not provided teaching that fusions to other sequences could be used as anti-inflammatory agents. *Id.* at 5. The Office also notes that "many cytokines are pro-inflammatory and they could exhibit opposite effects as the instant invention intends to have." *Id.*

Applicants respectfully assert that fusion proteins comprising (a) amino acid sequence comprising amino acid 42 to amino acid 60 of SEQ ID NO: 2, and, (b) a non-P selectin ligand amino acid sequence chosen from an antibody, an arabinogalactan protein, a bone morphogenic protein, and a cytokine are supported by the specification. As noted by the Office, the specification teaches fusion with the Fc portion of an antibody. *Id.* Fusions with an arabinogalactan protein, a bone morphogenic protein, and a cytokine are described in Example 15. Each of these fusion proteins contain the region of SEQ ID NO:2 sufficient for mediating P-selectin binding. A protein that comprises the amino acids sufficient for inhibiting P-selectin, even fused to the Fc portion of an antibody, binds ligand, and it is reasonable to expect that such fusion proteins would inhibit P-selectin binding regardless of additional amino acids.

The Office also rejects claims 58-71 asserting that Ulbrich et al. (Trends in Pharmacology, pp 640-647 (2003)) ("Ulbrich") teaches that a fusion protein of PSGL-1 failed in clinical trials *Id.* The Office objects to Applicant's submission of Wang et al., Journal of American College of Cardiology, Vol. 38(2): 577-582 (2001) ("Wang"), Gasser et al., Journal of American Society of Nephrology, Vol. 13: 1937-1945 (2002) ("Gasser") and Battistini *et al.*, Blood, 101(12): 4775-4782 (2003) ("Battistini"), referring to MPEP § 2164.05(a) which states that "Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing." *Id.* at 7.

Applicants did not submit Wang, Gasser and Battistini to show what was known at the time of filing. Applicants submitted these publications to demonstrate that the application was enabled at the time of filing, and that administration PSGL-1 and anti-PSGL-1 antibodies reduces inflammation. As noted previously, Wang discusses that P-selectin antagonism using rPSGL-Ig decreased neointimal hyperplasia following balloon injury by inhibiting inflammatory and thrombotic responses at the site of balloon injury while Gasser discusses that treatment with rPSGL-Ig prevented the early inflammatory changes in the transplanted organs. Battistini is able to block recruitment of $CD8^+$ T cells which express PSGL-1 to endothelium expressing P-selectin in multiple sclerosis patients, by using antibodies to PSGL-1, thereby reducing inflammation. Accordingly, these publications demonstrate that the claimed compositions are capable of reducing inflammation in a subject, as one of ordinary skill in the art would have predicted based

on the instant specification coupled with the information known in the art at the time of filing.

Ulbrich, which is itself a post-filing date publication cites to another reference published after the filing date, Diaz-Ricart *et al.*, Drugs of the Future, 27(4): 346-349 (2002), ("Diaz-Ricart"). As stated in MPEP § 2164.05(a) "[i]n general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling." As noted previously, Diaz-Ricart only discusses that the development of recombinant PSGL was discontinued for treatment of myocardial infarction due to disappointing results in clinical trials, but it expressly does not rule out the use of this molecule for treatment of other indications. *See*, column 2, page 348. Accordingly, the relevance of Ulbrich to enablement at the time the application was filed is dubious at best.

The Office concludes that "[w]hat is provided is merely an idea for an invention and clearly, further research was necessary in order to identify how it would actually be used." Office Action, 10/4/2006, p. 7. The Office concludes that undue experimentation would be required to practice the invention commensurate with its scope. *Id.* at 8.

Applicants respectfully disagree that undue experimentation would be required for the skilled artisan to practice the invention. The disclosure of the specification satisfies each of the Wands "enablement factors" enumerated by the Federal Circuit. *In re Wands*, 858 F.2d 731 (1988).

(1) The quantity of experimentation would be limited. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *Wands*, 858 F.2d at 736. Producing and testing the claimed fusion proteins would merely require following the teaching of the specification. The specification teaches numerous methods for studying the activity of PSGL-1 fusion proteins, including binding assays and cell-cell interaction assays. *See for e.g.* Examples 6 and 13. Such testing would be routine to the skilled artisan.

(2) The amount of direction and guidance presented is substantial, including the Examples, which provide extensive disclosure on how to make PSGL-1 proteins and test for their activity.

(3) The specification discloses working examples of PSGL-1 fusion proteins that inhibit interactions between PSGL-1 and ligand, including those of Example 13.

(4) The nature of the invention is in the biotechnological arts as was the invention found to be enabled in *Wands*. As noted above, the specification provides substantial guidance on the making and screening of PSGL-1 proteins.

(5) The state of the prior art indicates that production and testing of proteins was routine and that the claimed compositions have activities capable of reducing inflammation in a subject, as one of ordinary skill in the art would have predicted based on the instant specification coupled with the information known in the art at the time of filing.

(8) The breath of claims 58-71 is restricted to the use of fusion proteins and diseases specifically enumerated in the specification.

Applicants assert that the specification is fully enabled for claims 51-71 and request withdrawal of the rejection and allowance of the claims.

IV. Written Description Rejections under 35 U.S.C. § 112, first paragraph

The Office rejects claims 58-71 under 35 U.S.C. § 112, first paragraph for alleged lack of written description. The Office asserts that "[t]here is no teaching regarding the relationship of structure to function, such as how long these molecules are, what structural features are required for P-selecting ligand activity." Office Action, 10/4/2006, p. 9. The Office concludes that "the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the conjugation products that Applicant has disclosed." *Id.* The Office asserts that "there is not even identification of any particular portion of the structure that must be conserved," and that "in the absence of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus." *Id.* According to the Office, "the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides and conception is not achieved until reduction to practice has occurred." *Id.*

Applicants respectfully traverse the rejection of claims 58-71 for alleged lack of written support as the specification clearly teaches a relationship between the structure of P-selectin ligands and their function. The instant claims are directed to the use of fusion proteins comprising amino acids 42-60 of SEQ ID NO: 2. The amino acid

sequence of SEQ ID NO:2 is provided by the specification. The specification provides ample description of the relationship between this structure and the function of binding P-selectin. As noted by the Office, the specification describes the structure and function of several different fusion proteins, all of which contain amino acids 42-60 of SEQ ID NO: 2. *Id.* at 8. *Also see for e.g.* Figures 12, 16 and 21. The specification takes it a step further, not only providing binding studies of these fragments, but it describes the function of individual amino acids lying between amino acids 42 and 60 of SEQ ID NO:2. *See* Example 13 and Figure 30. The proteins of the claimed methods all include this region of SEQ ID NO: 2, which is a characteristic that distinguishes them from other proteins. Thus, the skilled artisan would envision a genus of peptides that all share the characteristic of having amino acids 42-60 of SEQ ID NO: 2, a structure that the specification teaches is sufficient for the function of binding ligand.

The instant case differs from *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) or *Amgen Inc., v Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). In *Amgen*, an alleged infringer asserted that he had invented the claimed DNA because he had developed a method for isolating it. *Amgen* 927 F.2d at 1205. The issue in *Fiers* was quite similar, with a party to an interference claiming priority of invention based on a method for isolating the DNA of the count. *Fiers* 984 F.2d at 1168. The Federal Circuit concluded in *Amgen* that "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated." *Id.* at 1206. The court reiterated this standard in *Fiers*. 984 F.2d at 1169. This standard is clearly met in the instant

case. The specification provides the sequence of the protein that is recited by the claims and describes numerous examples of species of P-selectin ligand proteins falling within the scope of the claims. Based on this disclosure, the skilled artisan would conclude that Applicants were in possession of the invention. See *Vas-Cath Inc., v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991).

Applicants believe that the specification as filed would convey to one skilled in the art that Applicants were in possession of PSGL-1 fusion proteins comprising amino acids 42-60 of SEQ ID NO: 2 and any non-P selectin ligand amino acid sequence. Nevertheless, in an effort to facilitate examination, Applicants have amended the claims to recite those fusion proteins specifically described in the specification.

Applicants assert that the specification fully supports claims 51-71 and request withdrawal of the rejection and allowance of the claims.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request withdrawal of these rejections and timely allowance of the pending claims. Should the Examiner have remaining questions or concerns regarding this application, Applicants request that the Examiner contact the undersigned at 202-408-4118 to schedule an interview to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 30, 2007

By: 

James P. Kastenmayer
Reg. No. 51,862
Tel: 202.408.4118